EXHIBIT

“B”

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF WEST VIRGINIA

CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 4 Cases*	

Julie Drolet, MD, FRCSC, FACOG, FPMRS

Expert Report on Prolift and Prolift +M

Background and Experience:

I am currently a practicing physician, licensed in the state of Pennsylvania. I obtained my medical degree from the University of Montreal Canada in 1988. I then went on to complete a residency in obstetrics and gynecology in 1993. In the following year, I did a one year minimally invasive laparoscopic and hysteroscopic fellowship in Clermont-Ferrand, France. I have obtained certification from the Canadian Medical Council, the Quebec Board of Specialties, the Royal College of Physicians and Surgeons of Canada and American Board of Obstetrics and Gynecology. In June 2013, the first year the certification exam was conducted, I became board certified in Female Pelvic Medicine and Reconstructive Surgery.

In 1994, I began my career in a group setting, tertiary center and university teaching hospital at Notre-Dame Hospital in Montreal Canada, where I practiced until August 1997. Through a recruiter, I found my way to York Pennsylvania joining a solo practitioner until he passed away in 1998. Since then I have been in a mostly solo practice. I have been teaching residents in obstetrics and gynecology since 1994. Early in my career, I devoted my interest mostly to gynecology with a special interest in urogynecology, focusing on pelvic pain, pelvic prolapse and incontinence. Initially I did include general obstetrics in my practice, which I stopped in 2008. I have performed most surgeries through a minimally invasive approach. By my training and experience, I am familiar with, laparotomy (open), laparoscopic and robotic techniques as well as vaginal approaches to prolapse and incontinence surgeries.

I have witnessed and participated in the evolution of our understanding of pelvic organ prolapse and incontinence. During my fellowship, the surgical treatment of pelvic floor prolapse and incontinence was innovative and the use of minimally invasive technique was very different than the traditional repairs I learned during my residency training. Since 1994 I have performed laparoscopic sacrocolpopexies, intra-peritonal colpopexies, para-vaginal repairs and Burch urethropexies. In our quest to help patients, keeping in mind decreased morbidity and mortality, I have also performed thousands of vaginal surgeries with and without synthetic mesh for pelvic organ prolapse including but not limited to colpocleisis, traditional anterior and posterior repairs, sacrospinous ligament fixation, uterosacral ligament colpopexies, mesh augmentation including Prolift and Prolift+M, and anti-incontinence procedures including retropubic and transobturator midurethral slings. I have also developed expertise in the management of chronic pelvic pain and other symptoms after both traditional repairs and mesh repairs.

Throughout the world, not just in the USA, there has been a need for better understanding of and better repair for techniques to treat pelvic organ prolapse. Vaginal surgeries performed 30 years ago had excessive failure rates for the treatment of urinary incontinence and were associated with high recurrence rate of pelvic organ prolapse or the repairs were so "tight." The traditional prolapse repairs did not permit intercourse and some were associated with an excessive rate of dyspareunia, as is the case with levator myorraphy, which we now avoid. Open laparotomy techniques for pelvic organ prolapse repair are associated with increased morbidity associated with wound infection, adhesions and injury to abdominal and pelvic organs, bleeding, increased pain, and longer recovery time. With our aging population, as well as the ever-increasing rate of morbid obesity, even the laparoscopic or robotic approach are placing patients at increased risks compared to a vaginal approach. It is with this understanding that the need to improve the durability of repairs has led to the notion of augmentation or reinforcement of the already weakened pelvic support.

I have used the Prolift device, starting in May 2005, and later on the Prolift+M. I am familiar with the professional education training and the information for these devices that Ethicon provided to surgeons, including IFU's, surgical videos, Surgical Technique Guide, Surgeon's Resource Monograph, powerpoint presentations, other training materials. I am also familiar with the Prolift patient brochures. I have also used other types of mesh. I am aware of the FDA public health notices of 2008 and 2011, and the 522 orders that followed in 2012. As a urogynecologist, it is my professional obligation to keep myself up-to-date with the current literature, including peer reviewed applications regarding synthetic mesh.

In preparation of this report, I have considered the published medical literature available along with the opinions, recommendations and positions of statement from various medical professional societies as well as governmental agencies. In preparation of this report, I have reviewed provided documentation, relied on my education, training, continued education and certification and own my own clinical experience and expertise. I hold all of the opinions offered in my report to a reasonable degree of medical certainty. I reserve the right to supplement my report upon reviewing additional information.

Overview of Pelvic Organ Prolapse:

Issues of pelvic prolapse and incontinence are increasing in prevalence in the United States and around the world as women are living longer. It is estimated from the Women's Health Initiative and various other studies that the prevalence of incontinence varies between 25 and 50%, and the prevalence of prolapse, although based on varying definitions, varies between 15 and 41%. Both can coexist and the incidence increases with age. It is estimated that 11% of women have a lifetime incidence of undergoing pelvic organ prolapse surgical repair. In 2010, market data showed that 260,000 women underwent surgery for stress incontinence, 80% were done transvaginally with synthetic sling mesh. Approximately 300,000 women underwent surgery for

pelvic floor prolapse either as in or outpatient, and approximately one third used mesh; of those, three fourths were performed using a vaginal approach. These figures are estimated to increase by nearly 50% over the next 40 years (Dieter, 2015). Risk factors for pelvic organ prolapse are well known, and include advancing age, race, menopause, connective tissue disorders, obesity, vaginal parity, and smoking. Studies have shown that concurrent pelvic organ prolapse surgery at the time of hysterectomy and pelvic organ prolapse as an indication for hysterectomy are significant risk factors for pelvic organ prolapse later in life (Lykee 2015). In a study evaluating data from 154,882 women who underwent hysterectomy for benign indications, recurrence of pelvic prolapse most often was associated the initial indication of prolapse for the hysterectomy.

Although pelvic floor prolapse is not an immediate life threatening condition, it is a medical condition that is much more than cosmetic. Prolapse can affect lower and upper urinary tract function, bowel and defecation, pelvic pressure or discomfort, as well as have a negative impact on sexuality. Overall symptomatic pelvic organ prolapse can affect quality of life in a substantial manner. Most women will not be aware of their prolapse until it descends to the hymen and beyond, or until the development of new symptoms. Pelvic pressure, discomfort with activities and the feeling of bulging within the vagina are frequently reported as the prolapse worsens. Some patients become uncomfortable with intercourse, not only due to a negative body image, but depending on the compartment prolapse and associated midline fascial defect, there can be forceful pressure directly onto the bladder or the rectum, increased forceful displacement of the prolapsed vaginal apex or uterus within the pelvis, causing intercourse to become physically uncomfortable and even painful. The cervical or vaginal mucosa, once descended below the hymen, comes in contact with the patient's underwear or pad. This can lead to irritation, ulceration, bleeding, abnormal discharge and chronic infection of the vaginal mucosa. Women have been known to put Vaseline, Crisco, olive oil, diaper creams and various over the counter creams and lotions as these symptoms progress.

Anterior wall prolapse, often presenting with concurrent apical prolapse, symptoms can include feeling of pelvic pressure or bulging, frequency, urgency and urinary incontinence. As the prolapse worsens, there may be an associated "kinking" of the urethra. These women may experience symptoms of hesitancy and difficulty urinating, sometimes needing to reduce the prolapse digitally to assist voiding. As the anterior vaginal wall and bladder continue to fall well below the hymen, bulging discomfort associated with sitting or activities may progress along with issues of incomplete bladder emptying, recurrent urinary tract infections, and kidney infections are more prevalent. If left untreated, retention, hydronephrosis and kidney damage can occur.

Posterior wall prolapse, symptoms include pressure or bulging symptoms with accumulation of stools within the protrusion, difficulty with defecation leading to excessive straining or assistance with splinting or fingering in order to empty out the rectal ampulla, as well as fecal

smearing and incontinence. Conversely, functional disorders such as chronic constipation or dyssynergic defecation (abnormal non-relaxation or spasms of the levator ani muscles during defecation), may coexist with a posterior defect but are often mistakenly attributed to a visible rectocele or perineocele. Surgical correction in these patients will often lead to good anatomical success without treating the underlying cause and will not meet patient's expectations.

At a minimum, pelvic organ prolapse symptoms are a quality-of-life issues which interfere with a woman's sense of well-being. As progressive bulging, urinary and/or fecal symptoms and odors develop along with their associated embarrassment, negative body image and/or painful intercourse leading to decreased interest in intimacy and eventually social isolation starts to occur. Women will gradually forgo trip outings, social gatherings, and even family outings. Women suffering from symptomatic pelvic organ prolapse also start to decrease their level of physical activity and exercise, decreasing their quality of life, but this can also lead to medical problems, weight gain and associated negative impact on overall cardiovascular health. Pelvic floor prolapse is not just a cosmetic issue, it is a well-recognized medical condition for which various forms of pessaries and belts have been described through the ages, until surgical options have been become available in the last two centuries.

Multiple studies have been conducted to evaluate the benefits of pelvic floor exercises (Kegels), but most have a short follow up and are underpowered. Although some show improvement in urinary stress incontinence and some protection in cases of stage I prolapse, none of these studies conclude that pelvic floor exercises have any benefits to treat organ descent below the hymeneal ring. Modern pessaries are made of silicone and are an option if the patient can be properly fitted, and is willing and able to care for the pessary. To defy gravity and keep the pelvic organs up above the hymen, not only at rest, but during time of straining, lifting, or physical activities, it must be larger than the vaginal introitus. The ability to correctly and comfortably fit a pessary is dependent on the vaginal dimensions and shape. This device also rests against the levator ani muscle complex, and for women with pelvic floor dysfunction, causes further spasms and pain. In most situations, due to the size of the pessary and its firmness, intercourse can be difficult with the device in place and women need to be able to remove it or have her partner willing to do so. Since the pessary also needs regular cleaning a woman must be able to remove it, or be willing to come to her physician's office or have a home care nurse pull the device out, clean it, inspect the vaginal walls and cervix, and finally reinsert the device. Despite these cleanings, women are encouraged to insert vaginal estrogen or low-dose antibiotic gel periodically. Without this, most will experience a greenish foul-smelling discharge due to bacterial overgrowth as this pessary resides in a non-sterile environment of the vaginal lumen. Although pessaries can be used long term in some women there is a high discontinuation rate over time. Women less than 65 years, desire for surgery and advanced posterior prolapse are independent factors for discontinuation (Ninivago, 2016). Despite a well-fitting pessary, previously continent women may become incontinent. One explanation is that once the prolapse is reduced and the vaginal angle repositioned, thus unkinking the urethra, stress urinary incontinence will be made clinically

evident. Another explanation is that mechanically the pessary can put pressure on the bladder causing irritative voiding symptoms, or by compressing directly the urethro-vesical junction, cause incomplete bladder emptying and abnormal voiding issues. Complications from pessary use include cervical and vaginal mucosa infection, ulceration and erosion of the underlying fibromuscular layer and organs. These incarcerated pessaries have also led to vesico-vaginal and recto-vaginal fistula with devastating consequences.It is no wonder most studies show that despite most women being able to be fitted with a pessary, after one year of use, less than half continue this mode of therapy and opt for a surgical intervention.

The debate for the optimal route of pelvic prolapse surgery has been going on for almost 100 years. Until the advent of laparoscopic and robotic surgeries for prolapse in the last 25 years, the risk of additional morbidity via laparotomy incisions has meant that the vaginal approach should be encouraged whenever possible. Unfortunately, some report the persistence, recurrence or de-novo prolapse to be as high as 60% within 1 year after native tissue repair (Whiteside, 2004). The optimal approach for the repair of pelvic organ prolapse is still not known. A surgeon must consider the type of prolapse, their own surgical skills and expertise as well as patient factors, including obesity, previous abdominal and pelvic surgeries and other medical co-morbidities, when deciding the route of surgery. Surgeons and patients must weigh the benefits of a less invasive (vaginal approach) and more durable repair (mesh vs. weakened tissues) against the potential commonly known complication of mesh erosion or exposure that can occur with any foreign body implant.

Obliterative surgery such as colpocleisis and colpectomy are the least invasive of all prolapse surgeries; however, these obliterative procedures should be considered on a select group of patients and reserved for women who are certain they will never want to be vaginally sexually active in the future. . Most of the recent published data are case series with few patients. There are reports of failures, stress incontinence and infection with pyometria. Uterine cancer, although not a direct complication of the surgery, may have a delayed diagnosis due to possible hematocolpos or difficulty establishing diagnosis, as vaginal access to the cervix or endometrial cavity is now impossible. Zebede (2013) reports low rates of surgical complications and excellent long-term results, even in the elderly.

Vaginal prolapse surgery to maintain a functional vagina without graft augmentation, essentially involves trying to reattach or correct a defect using the patient's own, already weakened tissue. The quality and strength of a patient's vaginal mucosa, ligaments and fibromuscular layers will influence the resilience and longevity of the repair as these are the same tissues that have failed and contributed to the prolapse in the first place. Unlike mesh, the quality of patients’ tissues is variable and significantly impacts the short-term and long-term success of native tissue prolapse repairs, often resulting in high recurrence rates.

The anterior vaginal wall is the most frequent location of both primary and recurrent prolapse. Even comparing standard anterior prolapse to standard plus mesh and to ultralateral anterior colporrhaphy with median follow up of less than 2 years, anatomical cure rates were disappointing (Weber, 2001). Other factors will influence recurrence including tobacco smoking, not just at the tissue level but with its associated chronic cough. The failure rates for these traditional repairs have been cause for concern as repeat surgeries, on a now older patient with increased medical morbidity, in a previously scarred vagina can cause even more overall morbidity. When one considers that women who undergoes pelvic floor surgery at age fifty, might live into her mid-eighties, most studies do not currently reflect the true long term effects of our procedures.

Abdominal and vaginal paravaginal repairs are surgeries that have been around for decades. In the last 25 years, surgeons have introduced the laparoscopic approach. They are intended to recreate the level 2 support at the Arcus Tendineus Fascia Pelvis (ATFP), which restores the mid vaginal physiological axis. It involves dissection to the pelvic sidewall bilaterally and demands constant visualization and vigilance to be able to position multiple permanent sutures through the lateral portions of the vagina and pelvic side wall. This surgery is most difficult in obese women, or women with hip mobility when preformed vaginally. Some of the risks of this procedure include the above and hemorrhage from the pelvic vasculature, nerve damage due to the extensive dissection throughout the fibromuscular layer, ureteral and bladder injuries. The vaginal paravaginal repair was recently quoted as a technique with “complication rates seem unacceptably high” (Brubaker, 2010).

Traditional posterior repair involves midline plication of the fibromuscular layer using interrupted delayed absorbable sutures, resection of excess vaginal mucosa and in most cases it is associated with a perineoplasty in which the diameter of the introitus is reduced. Although most studies have involved a small number of patients and short-term follow-up, traditional midline plication of the fascia is preferred over site-specific defect repair for success rate, and that the rate of dyspareunia is the same. Levator ani muscle plication has been associated with worse dyspareunia outcomes. Occurrence of post-op sexual dysfunction is well known and has been cause for concern after rectocele repairs especially if concomitant urethropexy of Burch (Weber, 2000). Symptoms of splinting, straining, incomplete evacuation and obstructive defecation present before surgery, may or may not improve post-surgical repair (Paraiso, 2001). Surgical repair of posterior prolapse does not assure complete resolution of symptoms (Sung, 2012). Straining was decreased from 74% pre-operatively to 23% post-operatively. Incomplete evacuation and obstructive defecation persisted in 19% and 14% of patients respectively. Splinting was found to still be present in 23% (compared to 56%) and was associated with a longer history of splinting before the surgical repair. Even native tissue repair, with or without associated hysterectomy, can lead to pelvic pain, dyspareunia (18-38%), issues with incontinence and all other general risks associated with surgery and anesthesia.

Vaginal native tissue procedures that suspend the apex include: Sacrospinous ligament fixation, where 2 to 4 permanent and/or delayed absorbable sutures are placed through the sacrospinous ligament lifting the vagina or cervix on the right side. This deviates the axis of the vagina posteriorly and laterally, usually to the right side. It is associated with a higher recurrence of anterior vaginal prolapse (28.8%) and stress urinary incontinence (Morgan, 2007). Complications include hemorrhage from the internal pudendal vessels or hypogastric venous plexus, nerve injury to the sciatic or pudendal nerves. Rectal and ureteral injuries can also occur. Moderate to severe buttock pain has been reported in 55.4% immediately post op and, although decreased in intensity, as many as 15.3% reported to have ongoing pain beyond 6 weeks. (Unger, 2014). Vaginal stenosis and dyspareunia (20-36%) can occur. Similar data have been reported for the uterosacral ligament suspension. Suture erosion as those are often synthetic/permanent, and granulation tissue are often seen (15-40%) with either procedure. Kasturi-2012, reported a 22% suture erosion when using permanent sutures. Sacrospinous suture related complications are reported in 36% of patients with 70% of symptomatic women requiring deep suture removal (Toglia, 2008). Iliococcygeal fascia repair is similar, but results in more posterior displacement of the vagina associated, with an increased risk of stress urinary incontinence and recurrence of prolapse of the anterior vagina.

McCall/modified McCall culdoplasty and High Uterosacral Ligament suspension involve either a hysterectomy or usually opening the vaginal cuff with intraperitoneal access. The vagina is then attached to the cardinal ligaments and uterosacral ligament as well as peritoneum. Complications include injury to the ureters (2-11%), suture erosions, infection with pelvic abscess, hemorrhage, bowel and bladder injury. Recurrence, or new prolapse can occur, as well as dyspareunia (22% for the modified technique are documented). The randomized controlled OPTIMAL trial evaluated the sacrospinous ligament versus uterosacral ligament for the correction of apical prolapse. Although they found no difference in complication rates or composite success (objective and subjective measures: defined success as no apical descent greater than one-third into the vaginal canal or descent of the vaginal wall below the hymen and no bothersome bulge symptoms and no retreatment), their success rates at only 2 years were 64.5% for the uterosacral ligament and 63.1% for the sacrospinous ligament suspension. Approximately 18 % of women experiencing bothersome symptoms and 17.5% developed prolapse below the hymen. Notably 16.5% of patients experienced a serious adverse event.

Unger (2015) reported a retrospective chart review that also included patients from the OPTIMAL and OPUS trial of 983 women who underwent an uterosacral colpopexy amongst other concomitant procedures reported a composite recurrent prolapse rate of 14.4% at only 6.9 months follow up. Granulation and suture erosion of the apical vaginal mucosa was reported at 10.7%. Their rate of ureteral injury was 0%, but they also reported a 4.5% rate for ureteral kinking that required surgical or radiological intervention. The 2015 Up-to-date report on surgical repair of vaginal apical prolapse mentions a dyspareunia rate of 36% in the sacrospinous ligament fixation (Kenton, 2015).

In the management of apical prolapse, abdominal sacrocolpopexy has long been regarded as having the most durable long term results, but with increased complications and longer convalescence. Bowel injury, ileus and post-operative obstruction are known complications of any abdominal surgery, along with abdominal wall infection (including cases of necrosing fasciitis), infection of the mesh leading to infection of the sacrum, disk and lower vertebrae (osteomyelitis) with devastating consequences.

A comprehensive review of abdominal sacrocolpopexy (Nygaard, 2004) reported intra-operative complications involving perforations of the bladder (3.1%), bowel (1.6%) and ureteral injury (1%). The incidence of hemorrhage and transfusions were 4.4%. Also, post-operative complications including wound herniation requiring repair (5%), transient ileus (3.6%), bowel obstructions requiring surgery (1.2%), and mesh erosions into the vagina and adjacent organs. The secondary analysis or the CARE trial (Whitehead, 2007) reports that 6% of the women suffered a small bowel obstruction or an ileus, and 1.2% required surgical management. In addition, painful intercourse after this procedure have been reported at 16% (Kenton, 2015). There are reports of de novo unprovoked vaginal pain in the absence of mesh erosion (Buechel, 2016). Removal of the abdominally placed mesh, even in this gold standard procedure for apical prolapse, involves high-risk surgery. Urinary incontinence is a well-known occurrence after sacrocolpopexy, even in previously continent women, over 45% will suffer from de novo urinary incontinence. It is now recommended to proceed with a prophylactic urethropexy or sling procedure. Despite this additional surgery, over 20% of women will still have problems with urinary incontinence (Brubaker-CARE trial, 2006). Mesh erosion rates were thought to be much lower than vaginally placed mesh, but tend to appear much later at a mean of 5 years (Aslam, 2016). This also is in line with the reported 10.5% mesh erosion at 7 years in the E-CARE trial (Nygaard, 2012). Even though the abdominal sacrocolpopexy is often considered the gold standard repair for apical prolapse, the CARE trial noted that “little is known about safety and long-term effectiveness” of this procedure. Sexual function after sacrocolpopexy is overall improved but the rate of de-novo dyspareunia is reported to be 14.5% (Handa, 2007). In the last few years the laparoscopic and more recently the robotic approach, appear to offer similar outcomes with decreased blood loss and decreased hospitalization (Siddiqui, 2012). These minimally invasive techniques may also be associated with decreased post-operative bowel complications (Nosti, 2014; Campbell, 2016). Many studies comparing abdominal to minimally invasive sacrocolpopexy are retrospective cohorts, and most were performed on women with an average BMI of 25 to 27. These results may not apply to the general patient population since the majority of women in the United States are overweight or obese. As noted in the most recent Cochrane review of apical prolapse surgery comparing abdominal to laparoscopic or robotic, the data reflects mostly post hysterectomy patients. The data on bowel complication was too few to accurately evaluate and most importantly, “not all women are suitable for sacrocolpopexy” (Maher, 2016).

In the same Cochrane review, six randomized controlled studies were considered to compare vaginal route to sacrocolpopexy. Overall, the patient awareness of prolapse and repeat surgery for prolapse is more than double after vaginal surgery. Although urinary stress incontinence was increased and estimated at 16.3 to 40% after vaginal suspension, compared to 13.9% after sacrocolpopexy, the repeat surgery for this did not reach statistical significance. It is important to keep in mind that most women undergoing sacrocolpopexy will also have concomitant anti-incontinence surgeries, but despite this, at 2 years 32% report incontinence and up to 45% reported incontinence in the group without concomitant Burch colpopexy (Brubaker-2008).

With better research and understanding, the key to a successful surgical prolapse repair is suspension of the apex, keeping in mind that the pelvic floor is a dynamic structure. Surgery in one compartment, by displacing the vaginal axis may place pressure/traction on other compartments that may also have been weakened, but not yet clinically visible or symptomatic at the time of the index surgery, and may cause prolapse or incontinence. Most pelvic floor surgeons consider level 1 support, as described by DeLancey, critical in the long-term success in maintaining the appropriate distribution of forces within the pelvis as well as prevention of recurrences of the initial surgery along with prevention of other compartment failures (Withagen, 2010).

Risk factors for recurrent POP after surgery include age, with a 3-fold increase if a woman is younger than 60 at her index surgery, as well as a more advanced prolapse stage (Whiteside, 2004). Other factors include obesity and chronic lifting or coughing, by increasing pressure directly on the pelvic floor, as well as multiple compartment prolapse. True incidence of prolapse recurrence is difficult to ascertain, as many studies have only a short-term follow-up and have lost patients to follow up. Traditionally, a 30 to 50% recurrence rates were used. Only in the last few years, have some reports described a less than 15% recurrence rate. This is in large part due to the definition of surgical success having been relaxed to include Stage II down to and including the level of the hymen, as well as more subjective QOL issues. By contrast,in many of the earlier studies, objective success was a more stringent outcome described at Stages 0-1. These “re-evaluation” reports still have limited length of follow-up, and many randomized studies are underpowered and contain incomplete data due to high rates of lost contact with patients.

Hysterectomy and Pelvic Pain:

Chronic pelvic pain including dyspareunia are problems that can affect 8 to 22% of women at some point in their life (Latthe, 2006).. In the United States, it is estimated that chronic pain syndromes affect 34% of all women (Brennan-2007). Crombie-1998 reported a survey of 5,000 patients seen in chronic pain centers found that 34.2% had pain from degenerative disease and 22.8% of patients complained of chronic pain after surgery, making it the second most common

complaint. Other U.S. based studies have shown a high rate of chronic pelvic pain, persistent dyspareunia, sexual dysfunction, and IBS amongst the general population of women (Mathias, 1996; Jamieson, 1996, Laumann, 2004).

Pelvic pain, both acute and chronic, is one of the most frequent complaints seen by gynecologists (Danielsson, 2003), and is often one of the most complex problems to treat due to the proximity of anatomically and embryologically organs, muscles and nerves.. Innervation to the upper vagina is complex as it derives branches from the spinal nerves S2-S4, pelvic splanchnic nerves, inferior hypogastric and pelvic plexus. The various causes of pelvic pain and dyspareunia are well-described in the medical literature (Eickmeyer, 2016; Aslan, 2008; Meana, 2015; Ferrero, 2008, Lowenstein, 2004).

Table 38-1 Possible Etiologies of Pelvic Floor Pain or Dysfunction by Medical Specialty

Gynecologic	Gastrointestinal/Genitourinary	Musculoskeletal	Psychological
Vulvodynia	Interstitial cystitis	Low back pain	Anxiety
Dysmenorrhea	Urgency/frequency syndrome	Lumbar radiculopathy	Depression
Endometriosis	Levator ani syndrome	Sacroiliac joint dysfunction	History of abuse
Fibroids	Bowel/bladder incontinence	Coccydynia	
Organ prolapse		Hip disorders	

Table 38-2 Pelvic Floor Musculature Anatomic Origins, Insertions, Innervation, and Function

Muscle	Origin	Insertion	Innervation	Function
Puborectalis	Pubic symphysis	Pubic symphysis	S3 to S5, direct innervation from sacral nerve roots	Raises the pelvic floor
Pubococcygeus	Posterior pubic bone and arcus tendineus	Anococcygeus ligament and coccyx	S3 to S5, direct innervation from sacral nerve roots	Maintains floor tone in upright position
Iliococcygeus	Ischial spine and arcus tendineus	Anococcygeal raphe and coccyx	S3 to S5, direct innervation from sacral nerve roots	Voluntary control of urination
Coccygeus	Ischial spine	Lower sacral and upper coccygeal bones	S3 to S5, direct innervation from sacral nerve roots	Support of fetal head
Piriformis	Anterior sacrum	Posterior surface of greater trochanter	S1 to S2 via nerve to piriformis	Lateral rotation, abduction of thigh; retroversion of pelvis
Obturator Internus	Pelvic surface of ilium, ischium, and obturator membrane	Posterior surface of greater trochanter	L5, S1 to S2 via nerve to obturator internus	Lateral rotator of thigh

Changes associated with aging contribute to painful intercourse in the peri and post-menopausal woman. The vaginal tissue loses its elasticity and natural lubrication is halted due to hormonal and vascular changes.

Even for the most experienced surgeons, pain with intercourse is one of the sequela of hysterectomy with or without concomitant surgeries. Post-operative dyspareunia can occur due to recurrence of conditions for which the hysterectomy was indicated, post-operative changes as well as pre-existing pain syndromes. De novo dyspareunia may occur in as many as 2.3% of women after undergoing hysterectomy, although the true incidence may not be known (Rhodes, 1999). Hyperalgesia or allodynia of the vaginal cuff suggest neuropathic dysfunction (Lamvu, 2004). Surgical factors include vaginal cuff closure as it relates to the approach to the

hysterectomy, vaginal versus abdominal/laparoscopic. Abdelmonem (2010) reported on a significant difference in the post-operative dyspareunia rate of 20% associated with vaginal hysterectomy for prolapse compared to 5% following total abdominal hysterectomy for other benign reasons. In the same study, vaginal length has been shown to be reduced by approximately 2 cm after a vaginal hysterectomy compared to the abdominal route. Pelvic organ prolapse in itself, can affect sexual function and many of these women will be offered a vaginal approach to their hysterectomy, which has been **encouraged by the American College of Obstetrics and Gynecology**, along with other concomitant vaginal procedures. The rate of dyspareunia is approximately doubled in vaginal hysterectomy compared to the abdominal route. Pelvic organ prolapse is associated with pelvic discomfort and sexual dysfunction (Dua, 2012). Post-operative dyspareunia after pelvic organ prolapse surgery with native tissue is reported to occur in approximately 14.5 to 36% of women. It is also noted that a vaginal hysterectomy may negatively affect sexual function although it is unclear if linked to length or caliber (Weber, 2000). The residual ovary can be implicated in causing deep dyspareunia when an elongated infundibulopelvic ligament suspends the ovary well below the pelvic brim, as encountered in uterine prolapse, deep in the pelvis and near the vaginal cuff. Post-operative adhesion formation caused by tissue manipulation during normal surgical procedures can result in pain. Nerve fibers are present within scar tissue even in the normal course of healing. Pain at the apical scar may be secondary to nociceptive sensation or reflect prior chronic pelvic pain. Dense adhesion causing organ immobility may also be associated with pain. Research looking at various risk factors for the development of post-operative chronic pain demonstrate a previous history of pain, anywhere, to be the biggest risk factor (Butrick, 2016). Chronic local or systemic pain syndromes involve central sensitization and increased upregulation and abnormal sensory processing.

Increasingly accepted as an etiology of pelvic pain, dyspareunia, voiding dysfunction, and defecation issues is dysfunction of the levator ani muscle group, especially the puborectalis and pubococcygeus muscles. Hypertonicity can cause severe proximal (introital), mid and/or deep dyspareunia, as well as discomfort or pain that can last hours or days after intercourse. Other symptoms include pelvic pressure and the sensation that pelvic organs are falling out. Women complaining of significant pelvic pain along with prolapse symptoms often have myofascial pain, out of proportion to the degree or severity of the prolapse. The reported prevalence of levator ani myalgia varies between 9% and 24%, and it has been noted that these women were significantly younger and reported a much higher symptom bother score on standard questionnaires. Also significant is the self-reported increased rate of fibromyalgia (OR 4.4), depression (OR 1.8), use of narcotics (OR 2.5) and prior sexual abuse (OR2.5) (Adams, 2013).

Voiding dysfunctions are common including urgency, frequency and feeling of incomplete bladder emptying, straining with urination and supra-pubic pain.

Defecation problems occur due to a paradoxical contraction of the levator ani muscle, while it should be relaxed. This obstructed defecation causes women to strain forcefully and over years contribute to rectal mucosal prolapse and worsen overall pelvic organ prolapse. This is often interpreted as constipation but does not respond to usual bowel remedies or prolapse repair. Fibers from S2-4 nerves, inferior hypogastric and splanchnic nerves give innervation to the pelvic musculature, pelvic organs and vagina. This complex anatomy may also explain associated low back and low anterior abdominal pain. Levator ani myalgia and spasms can contribute to, or result from, urethral irritation and/or urinary tract infections. Symptoms of urgency, frequency and feeling of incomplete bladder emptying are common. Over time this leads to straining to void and the development of stress urinary incontinence. A long history of bladder issues, dysuria or dyspareunia may exacerbate pelvic floor spasms further increasing the patient's symptomatology and pain. Treatment includes therapy by experienced physical therapists, specializing in pelvic floor and sacro-iliac disorders may include bio-feedback. In addition, medical therapies may include muscle relaxants, neuro-affecting drugs, vaginal Diazepam and intra-muscular injections with local anesthesia, steroids, and even Botox. In my practice, I refer 2 to 10 patients per week to pelvic floor therapy for the management of chronic pelvic pain, dyspareunia, voiding or defecation problems associated with levator ani muscle spasms and/or sacroiliac pain. Some of these patients have had a hysterectomy performed in the past for pain but are seeing me for persistent pain, and certainly, the majority of these women have never had any vaginal mesh surgery. All pelvic floor surgeries are associated with commonly known risks such as pelvic pain and dyspareunia, both of which can be temporary or chronic. Dyspareunia was described as a well know and accepted complication of vaginal surgery going back to the 1960s (Francis, 1961).

Painful Bladder Syndrome

Painful bladder syndrome, including interstitial cystitis are chronic conditions associated with urethral, bladder and pelvic pain, symptoms of urgency and frequency as well as dyspareunia in 50-90% of women with this condition. Women are five times more affected than men and the prevalence is reported to be approximately 4.3%. Although the exact etiology is unknown, theories include inflammation/injury to the GAG layer composing the inner lining of the bladder, which contributes to decrease pain threshold, bladder compliance and increased irritative voiding symptoms. The immune system response may be implicated as manifested by mast cells found along with nerve fibers in the urothelium along with epithelial dysfunction at the cellular level. One of the most frequent associations is a history of frequent urinary tract infections, although an initial UTI may be implicated in the etiology, no specific bacteria has been implicated. On pelvic examination, 78-85% of patients have associated levator myalgia (Bassaly 2011; Peters, 2007). Symptom exacerbation, or flare-ups are common and can last a few days to weeks. Over time, fear of pain will further contribute to pelvic floor spasms, avoidance of penetration and potentially decreased libido. Treatment involves long term management involving a multidisciplinary approach including dietary modifications, oral medications (antispasmodics, Phenazopyridine-AZO, neuromodulators, antidepressants, antihistamines, Pentosan-Elmiron), pelvic floor physical therapy & intravaginal diazepam, bladder instillations, cystoscopic

hydrodistension/treatment of Hunner's lesion, neuromodulation, and other more invasive surgeries. Chronic cystitis, trigonitis or urethritis are also contributors to pelvic pain. The urogenital organs are intimately linked. The bladder, trigone and urethra all rest on the anterior vaginal mucosa and are compressed and stretched during coital activity. This will be compounded by levator ani dysfunction and/or perineoplasty which further reduces the introital diameter.

Introduction of Mesh for Pelvic Organ Prolapse:

General surgeons began attempting to repair hernias with mesh in the 1950s, which started the evolution of various meshes and techniques using mesh repairs to provide more consistent and durable repairs in various parts of the body. The goal with using mesh in hernia repairs was to provide a more durable and consistent repair that surgeons and patients were not achieving with native tissue repairs. Gynecologic surgeons adapted mesh to the pelvic space to treat SUI and POP abdominally as early as the the1960s to reduce the failure or recurrence rates seen with native tissue repairs. To meet this need for a more durable repair, Ethicon and other companies then began to supply mesh for use in the pelvic surgery to satisfy the surgeon demand.

As described in the Librojo declaration, Ethicon submitted to the FDA its new drug application (NDA) for Prolene sutures in January 1966, which included required studies of the polypropylene suture. After a 3-year review, after meeting the requirements of the FDA, the agency concluded that Prolene was safe and effective for its intended use, and granted approval in April 1969. Prolene sutures then rapidly became the suture of choice for various surgeries involving tissues that required permanent sutures. Various changes to the labeling, approved by the FDA were made over the years to include warnings on "minimal transient acute inflammatory reaction," "resists involvement in infection" and that "it is not subject to degradation or weakening by the action of tissue enzymes". Such statements were supported by Ethicon submitted as part of the NDA and various supplements, as well as published medical literature.

In 1976, the FDA reclassified Prolene as a Class III medical device. Since it already had been used safely for more than a decade and because it had been approved as safe and effective by the FDA, it automatically had pre-market approval by the FDA.

In 1982, the FDA recommended that surgical meshes be classified into class II and this was upheld in 1988. By then, various surgical mesh had been widely used for more than two decades.

In 1990, polypropylene sutures were down classified to Class II due to their history of safe clinical use. Prolene mesh, knitted form the same monofilaments of Prolene, was also marketed in the mid 1970s, and because the FDA did not classify it as a drug, it also was included as a pre-amendment device.

In 1996, Ethicon submitted a 510(k) for Modified Prolene surgical mesh based on the predicated Prolene mesh and obtained clearance in August of the same year.

The FDA cleared Ethicon's Prolene Soft (Polypropylene) Mesh on May 23, 2000, followed by Gynemesh PS on January 8, 2002. Gynemesh PS is the same mesh that is used in the Prolift device, although rather than a flat sheet of rectangular mesh, the Gynemesh PS mesh used in Prolift was specially cut into a shape determined by the TVM group to be the ideal shape for prolapse repair. Ethicon regulatory affairs determined, based on an FDA guidance document, that since the Gynemesh PS mesh was already cleared, and the tools used with the insertion of Prolift were class I tools, that an additional 510(k) approval was not necessary. The FDA disagreed and requested that Ethicon submit a 510(K) add-to-file. The FDA granted Ethicon 510(k) clearance for both Prolift and Prolift+M in May 2008. Prolift+M was made from partially absorbable Ultrapro mesh (made from poliglecaprone (Monocryl) fibers and Prolene 3.5 mil fibers, which are the same sized Prolene fibers used in Gynemesh PS). As reported in Washington (2011), Ethicon's TVT mesh weighs 97 g/m2 and has a pore size of 1.1 mm. Gynemesh PS (the same mesh used in Prolift) is polypropylene and weighs 46 g/m2 with a pore size of 2.4 mm. Gynemesh +M is partially absorbable, substituting Monocryl for part of the polypropylene. Gynemesh +M weighs 58 g/m2 pre-implantation and 28 g/m2 after resorption of the Monocryl fibers. Maximum pore size is 2.5 mm before implant and 3.5 mm after resorption.

The introduction of mesh in the treatment of pelvic organ prolapse was intended to attain an important goal for surgeons - improve the longevity of the repair. In the 1970s more gynecologists were performing sacrocolpopexies using mesh to suspend the apex of the vagina. These surgeries were performed via laparotomy and although they had a high success rate and were considered the gold standard for apical prolapse repair, this procedure was associated with increased surgical and medical morbidity compared to vaginal surgery.

The types of mesh used for sacrocolpopexy have also evolved. The use of biologicals or cadaveric fascia has proven to be inferior to synthetic mesh. Mersilene, Marlex, and even Goretex mesh, have been used in the past but they present an increased risk of infection and erosion compared to Ethicon's Prolene and more recently developed Gynemesh PS mesh. Rates of mesh erosion are reportedly low between 3 to 5%, but these have been noted with only relatively short-term follow up. Nygaard has published a review showing mesh erosion rates from abdominal sacrocolpopexies to be as high as 12% and Nygaard's recent publication of the

extended CARE study reported mesh erosion rate of 10.5%, with lower rates reported for polypropylene meshes.

In the 1990s gynecologists were implanting mesh via the transvaginal route to reinforce their traditional prolapse repairs. These meshes had to be cut from larger pieces into segments tailored to the desired shape for each patient. Biological and synthetic grafts were introduced to many pelvic floor surgeons for augmentation of a pelvic floor defect such as cystocele or rectocele traditional repair. Unfortunately, their use in securing level 1 (apical) or level 2 (paravaginal) defects still required extensive dissection and visualization to affix or suture the mesh especially in the anterior compartment to the Arcus Tendineus Fascia Pelvis (ATFP). A need for a new approach to deliver this improved support was in great demand.

Pelvic floor surgeons in the 1990s and early 2000s were using a variety of instruments, tools, approaches, and meshes to accomplish transvaginal mesh repairs prior to any mesh convenience "kit" being available. There was a need for a standardized repair so that surgeons could compare their expected outcomes to those reported in the medical literature with a higher level of confidence. Prolift was the first to answer that call for many surgeons. In 2005, Ethicon introduced mesh kits containing a precut mesh as well as trocar delivery system introduced as a line extension to Gynemesh PS. Although the location of the tissue plane to dissect was different, as it needed to be deeper (full thickness) than the usual fibromuscular layer (fascia) that we used traditionally for a colporrhaphy, the training that was offered clearly demonstrated the relative ease of this entry into the correct plane and the importance of the full thickness dissection. The importance of placing the mesh behind this layer of fascia, which is essentially where the mesh is placed during sacrocolpopexy, was well recognized as the experiences with previous non-precut mesh demonstrated high rates of erosion when positioned superficially. Surgeons were also familiar with the route traversed with Prolift from performing sacrospinous ligament fixations.

The anterior Prolift is designed to re-establish mostly level 2 vaginal support, at the level of the arcus tendinous, with some component of level 3. The Posterior Prolift re-establishes level 1, 2 and possibly 3 support through a modified sacrospinous fixation technique. Compared to traditional unilateral right sided sacrospinous fixation, Prolift has better midline anatomical prolapse correction and rates of dyspareunia are equivalent (Halaska, Svabic, daSilveria).

Depending on the type of mesh used to treat pelvic organ prolapse, non-absorbable synthetic, biologic or absorbable synthetic, the risks of associated scarring, contraction, risks to adjacent organs, mesh erosions or exposures, and pain or painful intercourse have been well known to gynecologists, urogynecologists, and urologists who operate in the pelvic floor. These risks are also well known as they have been described extensively in the peer-reviewed medical literature. The bio-chemical properties of these implants are important but also each patient's own immune

and histological reaction can also influence healing, scarring, short and long-term outcome, similar to other prolapse surgeries. The Gynemesh PS mesh used in Prolift, and the more recent combination of approximately equal parts of polypropylene and absorbable Monocryl used in Prolift +M, are not defective just because a small percentage of patients experience mesh exposures or other known complications associated with pelvic surgery. They are both made from large pore, lightweight, Amid type I polypropylene mesh, which is considered to be state of the art and the most appropriate material to use for Urogynecologic repairs.

The Prolift+M was eventually developed by Ethicon to continue trying to innovate and continue to maintain efficacy and durability of prolapse repairs as seen with Prolift, while continuing to attempt to reduce the risks of complications. Substantial equivalence to synthetic mesh with the same indications had previously been demonstrated with the Prolift and information on the clinical performance had been published in the literature. Before the introduction of Prolift and Prolift+M, there had been very few randomized controlled trials evaluating vaginal prolapse repair surgeries. Before Prolift was introduced, most surgical techniques have been used for decades without any validation studies, and despite this, are widely performed and considered to be within the standard of care for primary treatment of prolapse. Since then, many RCTs and well over 200 clinical studies have been performed evaluating the safety and efficacy of Prolift and Prolift+M.

Retrospective studies comparing Prolift to Prolift+M demonstrated similar results regarding safety and efficacy. The more recent studies also consider quality of life and patient satisfaction as well as impact on sexual function on well validated questionnaires. Some studies have shown improvement in dyspareunia and patient satisfaction rates with Prolift+M. In fact, one study found similar complications between Prolift and Prolift+M, and concluded that “the use of a partially absorbable mesh is efficient and reliable with relatively low rates of re-intervention.” (Quemener, 2014). The authors also found that “a partially absorbable mesh does not seem to give advantages in comparison with classic non-absorbable mesh regarding rates of re-intervention.” Table 3 from Quenemer demonstrates similar complication rates between Prolift and Prolift+M.

Table 3
Comparing rates of reintervention at 12 and 18 months after placing prosthesis Prolift versus Prolift + M.

Indications		Prolift	Prolift + M	
Mesh-related complications including mesh exposure	12 months	2.3%	2%	NS
	18 months	2.5%	2%	NS
Mesh exposure	12 months	1.7%	2%	NS
	18 months	1.9%	2%	NS
Prolapse recurrence	12 months	0.8%	0.8%	NS
	18 months	1.7%	1.4%	NS
Urinary complications	12 months	4.6%	4%	NS
	18 months	5.3%	4.6%	NS
Total	12 months	7.2%	7.2%	NS
	18 months	9%	7.8%	NS

Mesh-related complications include mesh exposure, mesh infection, mesh retraction, rectal compression and symptomatic synechia. Urinary complications include TVT-O mesh exposure, de novo SUI, persistent SUI, recurrent SUI, voiding dysfunction.
NS: not statistically significant.

Early studies evaluating Prolift have shown 80-90% objective and subjective cure. The 12 month results from the French TVM study (which used the pre-shaped mesh but not the delivery system: guide and cannula) had a success rate of approximately 82%. The failure rate was 18.4% (absolute rate, with a 90% CI of 11.9-26.6) at 12 months, which is a significant improvement over native tissue repairs. Of the 16 failures, only one patient had prolapse ICS stage III, while 15 patients had prolapse of ICS stage II, with 10 of those 15 patients having stage II where the leading edge of the prolapse was at or inside the introitus. If one recalculates these failure rates, per the newer definition, at or above the hymen, then the actual success rate would be over 98%.

There have been several randomized trials comparing polypropylene mesh with traditional native tissue repair. (Hiltunen, Sivalslioglu, Nieminen x2, Nguyen, Carey, Withagen, Altman) These studies show at 12 to 36 month follow ups, a statistically significant improvement in cure rates associated with mesh (from 81-93%) compared to native tissue (48-72%), except Sokol which showed an improvement but not statistically significant, and Carey which also favored Gynemesh PS, despite its placement above the fibromuscular layer.

Table 1 Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	*p*
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

In addition to the studies in Table 1 found in the French TVM 5 year follow-up (Jacquetin, 2013), several other studies have evaluated Gynemesh PS or Prolift (which is made from Gynemesh PS) versus traditional repairs, including, but not limited to: Halaska (2012) showing 83.1% cure for Prolift and 60.6% cure for traditional repair, Da Silviera (2014) showing 88% cure for Prolift and 81% cure for traditional repair, and Svabik (2014) showing 97.2% cure for Prolift and 38.2% cure for traditional repair.

The TVM inventors continuously published their results on Prolift, and later on Prolift+M. In 2012, de Landshere and Cosson published a retrospective study of 524 patients with a median follow up of 38 months (15-63). Their reoperation rates for recurrence of prolapse was 3%, mesh erosion requiring surgery was 3.6% with mean time of exposure at 13 months. Their rate of mesh infection was 0.2%, and their rate of severe symptomatic mesh retraction was 0.4%. A similar study by Cosson using Prolift+M showed similar results.

In 2013, professor Jacquetin published a 5-year prospective study evaluating the clinical effectiveness and complication rates of total transvaginal mesh. Their definition of success was the leading edge above the hymen, no bulge symptoms and no reintervention for prolapse. At 1, 3 and 5 years respectively, this was 90%, 88% and 84% for all 3 criteria. While the rate of mesh exposure was 16%, only half required surgical intervention, with most of them within the first year. Their rates of de-novo dyspareunia were 10% but none at the 5-year mark. As for overall factors influencing sexuality, they are difficult to quantify over time as women and their partners continue to age and confounding physical, health and emotional factors are introduced.

The literature commonly reports that 8 or 9 out of 10 women reported that Prolift improved their quality of life. It is important to also consider the pre-existing dyspareunia and pain rates compared to the post-operative complaints of de novo dyspareunia and pelvic pain. For example, Yesil (2014) reported an improvement of dyspareunia in 17.8% of patients at 12-month

follow-up with a de novo dyspareunia rate of 10.7%. Some of the studies published through 2009 that reported dyspareunia rates include, but are not limited to the following: Fatton/Jacquetin (2007) reporting 2 patients with dyspareunia at 12 month follow-up; Paplomata (2007) reporting 2 patients with dyspareunia at 21 month follow-up; Van Raalte/Lucente (2007) reporting 22 patients (6.3%) with vaginal pain causing dyspareunia at 6 month follow-up; Hinoul (2008) reporting 3 patients with dyspareunia at 48 month follow-up; Lowman (2008) reporting 17% dyspareunia at 7 month follow-up; McEvoy (2008) reporting 4% dyspareunia at 18 month follow-up; Mobley (2008) reporting no patients with de novo dyspareunia at 24 month follow-up; Rechberger (2008) reporting 4 patients (19%) dyspareunia at 12 month follow-up; Van Raalte (2008) reporting No patient with dyspareunia at 12 month follow-up; Milani (2009) reporting 2 out of 11 patients (18%) with de novo dyspareunia but 2 out of 7 patients who had dyspareunia before the surgery but not after; Wetta (2009) reporting 2 patients (4%) with dyspareunia and 2% mesh exposure at 12-month follow-up. In a randomized controlled study comparing anterior Prolift to traditional repairs, Altman (2011) reports a 1 year composite success (Stage 0-1 and no bulge symptom) rate of 60.8% and 34.5% respectively. Looking only at anatomical success, it is 82.3% for Prolift and 47% for native tissue repair. The OR time and blood loss were greater in the mesh group, at 52 minutes and 82ml, but were not medically relevant or associated with complications. PISQ scores, rates of dyspareunia or pelvic pain did not reach statistical significance.

Studies have reported that women were satisfied with the outcome of their Prolift procedure even when they experienced a complication, such as mesh exposure or dyspareunia (Lowman, 2008). For example, Feiner (2010) reported 4 patients with de novo dyspareunia and 21 women reported an increase in sexual intercourse after Prolift; however, 94% of women saying that they would have chosen to undergo Prolift surgery again and 92% would recommend it to a friend.

Some of the larger patient population Prolift studies reporting on mesh exposures include; Meschia (2007) reporting 4.8% mesh exposure out of 228 patients at 6 months; Abdel-Fattah (2008) reporting 11% mesh exposure out of 219 patients at 3 months; Cosson (2008) reporting mesh exposures in 3 patients (1.8%) when uterus had been kept, 1 patient (2%) after previous hysterectomy, and 1 patient (4.3%) among patients with concomitant hysterectomy; Dedet (2008) reporting 2.6% mesh exposure out of 114 patients at 12 month follow-up; Lowman (2008) reporting 16.3% mesh exposure out of 129 patients at 7 month follow-up; Aungst (2009) reporting 3.8% mesh exposure out of 335 patients; Elmer/Altman (2009) reporting 26 (11%) mesh exposures out of 232 patients at 12 month follow-up, of which surgical intervention occurred in 7 cases and the remaining cases were all managed conservatively using topical cream; Ehsani (2009) reporting 2.2% mesh exposure out of 451 patients at 11 month median follow-up, of which 4 were treated surgically and the other 6 were managed conservatively with estrogen cream.

Longer term studies are appearing in the literature of mesh surgery. Benbouzid (2012) reported a 4.5-year follow up of patients who underwent various Prolift surgeries. As success was defined by Stage 0-1 with no retreatment in any compartment, was 85.3%, corresponding to low PDFI symptom score. Their reported mesh erosion in 5.3% of women. In a Prolift study with 5-year follow-up, the anatomic cure rate was 80.26%. (Ubertazzi 2015). There were 15 (19.74%) cases of prolapse recurrence. After 5 years of follow-up, only 4 patients (5.5%) required new surgery for POP, one of which was de novo. Mesh exposure was documented in 12 patients (15.8%), of which 6 patients required surgical resection and the remaining 6 patients were treated in the office and remain asymptomatic. De novo dyspareunia occurred in 2 patients (5%). Regarding subjective cure, 71% of patients considered themselves cured, 21% improved, and 93.5% would recommend the surgery. In a randomized controlled trial evaluating Prolift versus conventional native tissue vaginal repairs in patients with recurrent pelvic organ prolapse with long-term follow-up at 7 years, the overall anatomic success was higher in the mesh group, which was particularly significant for the anterior compartment (74% vs. 31% p 0.001) (Damoiseaux 2015). The de novo dyspareunia rate was 3/29 (10%) for the Prolift group and 3/26 (12%) for the native tissue group ($p = 0.328$). Heinonen (2016) looking at 7 year-median follow up. Of the initial 195 patients, 161 were still available. The anatomical success rate was 56.4% or 69.3% depending of the criteria. Reoperation for any compartment prolapse was 16.2%. Most importantly, is that 80.1% of women were still satisfied with their procedure. These long-term studies confirm that Prolift is safe and efficacious.

Studies involving Prolift+M have also reported good overall outcomes. Khandwala (2013) reported on a prospective cohort of 157 women treated with Prolift+M (3.2% anterior, 30.6% posterior and 66.2% total mesh), with mean follow up of 13 months. Composite success was 88% (94% if stage II was included). No visceral injuries occurred and de-novo dyspareunia was reported in 6% of women. Milani (2011) reporting on a cohort of 128 women, using a defined success rate as Stage 0-1 in 77.4%, but if we include the more recent definition at the level of the hymen, success was 89.5% at 1 year. Eighteen women (29.5%) had baseline dyspareunia, with resolution in 14 patients. De-novo dyspareunia was reported in 2% and mesh exposure rate was 10.2%. Significant improvements in quality of life and sexual function were found and 86.2% indicated they were “much better”. Following this, Lucente (2012) presented their 3-year outcome, with 75.9% success in the treated compartment (88% if considering hymen as limit). Cumulative mesh exposure was 14.8% (varied depending on hospital sites: 0-20%) with the majority occurring within the first year and with total pelvic mesh. De-novo dyspareunia was reported in 9% patients, but preexisting dyspareunia resolved in 33%. As important is the overall maintained improved patient outcomes, pelvic symptoms and sexual function as reported on validated questionnaires.

Studies on Prolift+M include a 1 year follow up on 127 patients with anatomical success at the hymen of 89.5% and that 96% felt that their prolapse was “better”, of those, 86.2% reported feeling “much better” (Milani, Cosson et al, 2011). Of the 61 patients who were sexually active

before surgery, 18 reported dyspareunia pre-op. Post-operatively 13 of these reported resolution of their pre-existing dyspareunia, 4 experienced persisting dyspareunia and one stopped sexual activity for unrelated reasons. Only 1 patient (2%) reported de novo dyspareunia at 1 year. Nine women who were not previously sexually active did resume intercourse without de-novo pain. Mesh exposure rates was 10.3%. Of these, most 11/13 were in patients with Total Prolift+M and 2/13 were Anterior Prolift+M. Treatment was conservative with vaginal estrogen cream in 6 patients. At 3 years, 96.9% of women were available for follow up and these same authors reported success in the treated compartment to be at 88%. A total of 19 patients (14.8%) had mesh exposure during the entire study period. This compares with previous literature on mesh exposures. Of the women with baseline dyspareunia, 6 (33%) resolved and de novo dyspareunia occurred in 3 (9%) women. They reported that "no major safety concerns were identified and that the low incidence of pain and dyspareunia are encouraging". Other comparable results have demonstrated the efficacy and safety of Prolift+M (Khandwala, 2013 - Lensen, 2013 - Bhatia, 2012 - Milani, 2012 - Khandwala, 2011 - Pizarro, 2011). In 2013 Khandwala and his group did not find clinical mesh retraction or a statistically significant decrease in total vaginal length after a 1 year follow up. Their reported rate of mesh exposure was only 2.2% at 1 year. Several retrospective or observational studies have found lower rates of dyspareunia, mesh exposure as well as decreased re-operations when comparing Prolift+M to Prolift (Bhatia, 2012 - Lensen, 2013 - Milani, 2012). We also realize that surgical experience and surgical volume are factors influencing risk and success of any surgical technique. Authors suggest that the decreased complications in the studies involving Prolift+M may be partially attributable to the experience gained by previous years of performing surgeries using Prolift. Studies have shown an inverse correlation between complications and surgeon volume. Patients of high-volume surgeons experience decreased rate of complications compared to low-volume surgeons (Withagen, 2011 - Welk, 2015). An analysis of 5,488 women undergoing pelvic mesh surgery, Kelly (2016) initially found that high volume surgeons (greater than 75th percentile) did not have less complications than low volume surgeons. Once the criteria changed to 90th percentile or "very high volume", representing 14 cases per year, an absolute risk reduction of 1.85% was found.

Mesh exposures typically appear within the first few months to 1 or 2 years (Quiboeuf, 2015- Firoozi, 2012- Kasyan, 2012) post-operatively and typically occur at the incision line. Furthermore, Benbouzid (2012) reported 85% cure and 5.3% mesh exposure rate at 4.5 year follow-up; Krcmar (2011) reported 83% cure and 3.78% mesh exposure with mean time to exposure being 12 months at 5-6 year follow-up; Gad (2012) reported 91.6%-100% cure and no mesh exposures at 5 year follow-up; Kozal (2012) which reported 4 mesh exposures out of 116 patients at 5 year follow-up; Popov (2012) showed 5.8% mesh exposures out of 1,311 women at 4 year follow-up; Wang (2013) reported 93% cure and 5 mesh exposures out of 80 patients at 3 year follow-up. Aslam (2016) compared the difference in time to mesh exposure between mesh placed abdominally versus vaginally and found a statistically significant difference. The mean time to exposure for abdominally placed mesh was 59.8 months compared to 23 months for vaginal placement ($p \leq .0001$). This is of importance in reporting comparative mesh exposure rates, when considering short term studies.

In two previous Cochrane reviews of 2004 and 2011 the authors concluded that the wide variety of surgical options available, indicated the lack of consensus as to the optimal treatment, and that no clinical guidelines existed that could identify the preferred surgical intervention.

In the 2016 Cochrane review (Maher et al,) comparing transvaginal mesh to native tissue repair, the authors commented on the FDA's concerns related to dyspareunia and vaginal pain that accounted for one third of the complications reports. Contrary to this, "surgery for vaginal pain or dyspareunia was barely mentioned". They included 25 RCT involving permanent mesh, comprising a total of 2500 women. These studies included those with as little as 20 women in each arm, and average follow up of 1 to 3 years. For their primary outcome: recurrent prolapse was defined as any stage 2 or greater (so even prolapse at or 1cm above the hymen was considered failure), repeat surgery for prolapse, for stress incontinence and a composite that included the latter two combined with mesh exposure. Only SIX studies involved Prolift. Others involved different mesh kits or tailored mesh, mesh overlay above the fascia (Carey, 2009) and multifilament mesh. Some included studies were underpowered (Iglesia, 2010 – Gupta, 2014). The actual definition of recurrent prolapse was different for daSilveira (2014): below the hymen, and was not defined in the study of De Tayrac, (2013).

The authors found that the awareness of prolapse was less likely with mesh, the rates of repeat surgery for prolapse were lower in the mesh group. Similarly, when comparing absorbable mesh to native tissue repair, the authors found that recurrent prolapse on examination was less likely in the mesh group. The recurrent prolapse rate was 38% in the native tissue repair compared to permanent transvaginal mesh, estimated range to be 11-20%, and the benefit was more pronounced in the anterior mesh group. None of the studies reported on the apical compartment. Predictably the risk of composite surgery, including mesh exposure was less in the native tissue (5%) compared to an estimated range of 7-18% in the permanent transvaginal mesh, mostly due to mesh exposures. There was no mention of granuloma or suture exposures related to native tissue repairs as few studies reported on apical suspension. The reported risk of mesh erosion was 10% in the anterior repair only and 17% in multi-compartment repair, overall 8% had surgery for mesh exposure. The rate of de novo stress urinary incontinence was reported at 10% with native tissue compared to the estimate of 10-17% with transvaginal permanent mesh repair, but there was no difference in the rate of post-operative surgery for incontinence in either group. We must remember that in the conventional/traditional/gold standard sacrocolpopexy, the rate of post-operative stress urinary incontinence is 40-60% without prophylactic anti-incontinence surgery. There was no difference in either group as to quality of life, sexual function, PISQ questionnaires and voiding disorders. There was no difference in the rates of de novo dyspareunia when comparing nonabsorbable mesh to native tissue repair. They did admit to the finding of multiple biases within the different studies along with incomplete data, heterogeneity between study groups, underreporting of allocation of randomization, blinding and selective reporting. They did not include many of the cohort studies and other non-randomized studies that could have significantly increased the total number of patients and longer term follow-ups. Their

definition of prolapse recurrence was stage 2 or worse. This means that any recurrent prolapse at the level of the hymen or up to 1 cm above the hymen was considered a failure. This definition is different than the definition adopted by many physicians, investigators and reviewers over the last few years. The authors conclude that the risk benefit profile has limited utility in primary surgery, but admit that in women with higher risks of recurrence, it is possible that the benefits may outweigh the risks, although not supported in their current review.

A Second Cochrane review by Maher et al, was published later in 2016 comparing surgeries for apical vaginal prolapse, with follow up of 1 to 4 years. Comparing native tissue vaginal repair to sacrocolpopexy, they found a 14% risk of awareness of prolapse, a 5-18% risk of repeat surgery for prolapse, 31-63% recurrent prolapse, increased risk for stress urinary incontinence and an increased risk of dyspareunia between 11-50%. Six randomized controlled studies were included comparing vaginal native tissue with vaginal mesh surgery. There was no statistical difference in awareness of prolapse based on 1 study involving only 54 patients and no difference in the rates for repeat surgery for prolapse. The do caution that the CI was wide and they noted “serious inconsistencies between studies”. The risks of stress incontinence, de-novo stress incontinence or surgery for stress incontinence were no different. Moderate quality evidence showed that there was “little or no difference” in de-novo stress incontinence, urgency incontinence, voiding dysfunction, PISQ or overall dyspareunia.

As described in Lowman (2008), the risk of de novo dyspareunia with Prolift is similar to what has been reported with traditional prolapse procedures. Multiple Cochrane Reviews and meta-analyses have demonstrated that mesh-based repairs have a statistically significant improvement in objective cure rates in the anterior compartment, and no difference in quality of life or complications such as dyspareunia compared to traditional procedures.

The Prolift IFU associated with the original launch in 2005 (which came with the Technique Guide), includes warnings and precautions as well as adverse reactions typically associated with surgical implant about materials including: infection, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that results in implant contraction. Further, the IFU mentioned punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during Gynecare Prolift guide passage and may require surgical repair. These are the risks that are specific to the device. These risks can all potentially lead to well-known symptoms of pain or dyspareunia after any prolapse surgery. Pelvic floor surgeons would know of the risks associated with any surgery including pain and dyspareunia by way of their basic medical education and training. They would also know that pain and dyspareunia are potential risks from infection, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that results in implant contraction and that these potential complications may need reparative surgery. Importantly, complications specific to the device, primarily, mesh erosion and scarring

that can results in implant contraction, have been included in the IFU since Prolift was first launched.

Also published and made available to physicians are the 2005 and 2007 Prolift pelvic floor repair system slides and the 2007 Prolift surgeon's resource monograph, which clearly demonstrate the proper placement of the guide and cannulas. They also discuss the increased risks of adding a concomitant hysterectomy as well as mesh complications including mesh exposure and erosion as well as dyspareunia and vaginal pain and many others, in addition to the treatment of complications.

In addition to Ethicon's IFU/Surgical Technique Guide/Surgeon's Monograph/ and Professional Education, the medical literature also describes increased risk of mesh exposure and recurrent prolapse with concomitant hysterectomy. For example, in Gani (2009), the authors concluded that, "concurrent vaginal hysterectomy is associated with increased risk of vaginal mesh erosion," The authors reported a mesh erosion rate of 13/127 (10.2%) with significant correlation between mesh erosion and concurrent vaginal hysterectomy (p=0.008) and a dyspareunia rate of 2.4%. These figures are consistent with more inclusive literature reviews. Feiner/Maher (2009) reported Prolift mesh erosion rate of 7% and dyspareunia rate of 2% from 8 studies and 1,295 women. The SGS review (Abed 2011) also reported similar results, finding a 10.3% mesh erosion rate.

Most common complications of Prolift & Prolift+M are known, acceptable and manageable. Even complications requiring surgical management are often successful without having to dissect the entire arms of the mesh (Firoozi, 2012). Fortunately, serious life threatening complications are rare. It is important to remember that dyspareunia and pelvic pain are common conditions in the general population. A WHO systematic review (Lathe, 2006) estimates that the world-wide prevalence of chronic pelvic pain is 2-24% and 1 in 5 women between the ages of 18-50 report pelvic pain longer than 1 year's duration (Howard, ACOG bulletin 2004). Some studies suggesting 40-50% of women have some form of dyspareunia or chronic pelvic pain at some point in their lives, regardless of whether they have ever sought surgical treatment for pelvic organ prolapse or stress urinary incontinence using mesh. These complications have been documented in the literature well before Prolift or Prolift+M became available.

In a 2-year follow-up study comparing mesh complications in the United States after transvaginal mesh repairs versus abdominal or laparoscopic sacrocolpopexy repairs, the authors concluded that "pelvic pain and dyspareunia are common complaints after prolapse surgery by any of the three approaches studied." (Dandolu 2015). The review included **29,201** patients with transvaginal mesh, **8,112** patients with laparoscopic sacrocolpopexy, and **5,094** patients

with abdominal sacrocolpopexy. The rate of dyspareunia was higher with sacrocolpopexies than transvaginal mesh cases. In a Prolift 8-year review study of 82 patients from a single center, most mesh complications were resolved in a single operation (Anderson, 2015). The authors found that subsequent surgical repair for incontinence or prolapse was needed in a minority of patients. More recently a retrospective cohort study of 245 women compared reoperations after robotic assisted sacrocolpopexy and transvaginal mesh for apical prolapse. They found no difference in the rate of reoperation for mesh exposure (Martin, 2015). In a retrospective chart review, Miklos (2016) reports on 445 patients underwent mesh removal from 2011 to 2013, from slings (56.5%) and pelvic prolapse mesh (43.5%) including sacrocolpopexy and transvaginal mesh. They conclude that "overall, sling, TVM, and sacrocolpopexy mesh removal are safe procedures when performed by experienced surgeons.

No matter the approach, all gynecologists are or should be aware of the surgical risks such as bleeding, infection, injury to nerves, organs and vessels, and post-operative risks including scarring, wound complications, painful intercourse (short and long term), pelvic pain (limited or chronic), urinary or bowel problems, long-term failure of the surgical site or other compartments, and the need to re-operate. All those risks are addressed in the medical literature and taught in residency and fellowship programs.

On October 20, 2008, the FDA issued Public Health Notification, to surgeons, practitioners, and consumers regarding the use of mesh from a wide range of manufacturers for the repair of pelvic organ prolapse and stress incontinence.

FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence

Issued: October 20, 2008

Dear Healthcare Practitioner:

This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI). Although rare, these complications can have serious consequences. Following is information regarding the adverse events that have been reported to the FDA and recommendations to reduce the risks.

Nature of the Problem

Over the past three years, FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These mesh devices are usually placed transvaginally utilizing tools for minimally invasive placement.

The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.

Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.

Recommendations

Pelvic floor surgeons were the target audience of this notification and would have been expected to read and consider this notice. Further, this notice was also discussed in a variety of other publications in the medical literature as well as Ethicon's Professional Education.

The FDA's Public Health Notification of 2008, warned surgeons of risks such as: erosion of the mesh "through the vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and or incontinence." Additionally, the FDA notice warned that "there were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases vaginal scarring and mesh erosion lead to significant decrease in patient quality of life due to discomfort and pain, including dyspareunia". Further, FDA recommended that physicians should:

- •Obtain specialized training for each mesh placement technique and be aware of its risks,
- •Be vigilant for potential adverse events from the mash especially erosion and infection,
- •Watch for complications associated with the tools used in transvaginal placement, especially bowel bladder and blood vessel perforations,
- •Inform patients that the implantation of surgical mesh is permanent and that some complications associated with the implanted mash may require additional surgery that may or may not correct the complication.
- •Inform patients about the potential for serious complication and their effect on the quality of life including pain during sexual intercourse, scarring, and narrowing of the vaginal wall.
- •Provide patients with a written copy of the patient labeling from the surgical mesh manufacture, if available.

A reasonably prudent pelvic floor surgeon performing incontinence and prolapse surgeries would have already been aware of the potential for these complications to occur with mesh, but would have been put on notice of the frequency of those complications outside of what was already reported in the peer-reviewed medical literature.

Patient brochures are intended to help provide an overview of the medical condition and help to initiate the conversation between the surgeon and the patient about treatment options. The Prolift Patient Brochure that was available to surgeons in late 2008, following the FDA's October 20, 2008 Public Health Notification, discussed risks of the Prolift in the "What are the risks?" section of the Patient Brochure (Eth.Mesh.03906037-52), which states:

> What are the risks?
>
> "All surgical procedures present some risks. Complications associated with the procedure include injury to blood vessels of the pelvis, difficulty urinating, pain, scarring, pain with intercourse, bladder and bowel injury. There is also a risk of the mesh material becoming exposed into the vaginal canal. Mesh exposure can be associated with pain during intercourse for the patient and her partner. Exposure may require treatment, such as vaginal medication or removal of the exposed mesh."
>
> "Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss the decision to have surgery with your doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition."

Ethicon communicated the above-mentioned warning language, which includes risks that are well known to physicians and pelvic surgeons. The communication of these risks and benefits appears to be reasonable, comprehensive and proper. Materials like this cannot summarize the vast body of available medical literature, and it is up to the operating surgeon, consistent with his or her training, experience, continuing education and up to date literature, to discuss the options for their individual patient and have an informative process with her.

The Prolift IFU (Eth.Mesh.02341454-1521) that would have been in effect through 2009 suggests that surgeons attend the Professional Education that Ethicon has made available to them at no charge, and included the following warnings to the pelvic floor surgeons who would have been qualified by their licensing boards and hospitals, and hopefully their own competence and confidence in their ability to perform the Prolift procedure:

> ADVERSE REACTIONS
>
> • "Potential adverse reactions are those typically associated with surgically implantable materials, including infection potentiation, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that results in implant contraction.
>
> • Punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during GYNECARE PROLIFT Guide passage and may require surgical repair."
>
> WARNINGS AND PRECAUTIONS
>
> • "Users should be familiar with surgical procedures and techniques involving pelvic floor repair and nonabsorbable meshes before employing GYNECARE PROLIFT Pelvic Floor Repair Systems.
>
> • Acceptable surgical practices should be followed in the presence of infected or contaminated wounds.
>
> • Post-operatively the patient should be advised to refrain from intercourse, heavy lifting and/or exercise (e.g. cycling, jogging) until the physician determines when it is suitable for the patient to return to her normal activities.
>
> • Avoid placing excessive tension on the mesh implant during handling.
>
> • Refer to the recommended surgical technique for the GYNECARE PROLIFT Pelvic Floor Repair System for further information on the GYNECARE PROLIFT procedures.
>
> • The GYNECARE PROLIFT Pelvic Floor Repair Systems should be used with care to avoid damage to vessels, nerves, bladder and bowel. Attention to patient anatomy and correct use of the device will minimize risks.
>
> • Transient leg pain may occur and can usually be managed with mild analgesics.
>
> • Do not manipulate the GYNECARE PROLIFT Retrieval Device with sharp instruments or cut it to alter its length."

Additionally, Ethicon's Prolift Surgeon's Resource Monograph would have been available to surgeons in 2007. The Prolift Monograph further informs surgeons about patient selection,

preparation, surgical technique, hydrodissection, full thickness dissections, complications such as dyspareunia and vaginal pain, mesh complications (erosion, exposure, and extrusion), and provided a summary of early clinical data. The Monograph correctly notes that complications are likely to be related to the surgeon's experience and technique, in addition to individual patient factors. Not surprisingly, studies have shown improvement in success and complication rates as surgeons advanced in the learning curve.

Similarly, the 2009-2012 Prolift IFU and Prolift+M IFU suggested that surgeons attend the Professional Education that Ethicon has made available and included the following warnings to the pelvic floor surgeons who would have been qualified by their licensing boards and hospitals, and hopefully their own competence and confidence in their ability to perform the Prolift+M procedure. Following the FDA's 2008 Public Health Notification, the Prolift and Prolift+M IFUs included the following warnings:

> ADVERSE REACTIONS
>
> • Potential adverse reactions are those typically associated with surgically implantable materials of this type, including hematoma, urinary incontinence, urinary retention/obstruction, ureter obstruction, voiding dysfunction, pain, infection potentiation, wound dehiscence, nerve damage, recurrent prolapse, inflammation, adhesion formation, fistula formation, contracture, scarring and mesh exposure, erosion or extrusion.
>
> • Punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during GYNECARE PROLIFT Guide passage and may require surgical repair.
>
> • Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pelvic pain or pain with intercourse. These may resolve with time.
>
> • Dissection for pelvic floor repair procedures has the potential to impair normal voiding for a variable length of time.
>
> WARNINGS AND PRECAUTIONS include some of the following
>
> • Users should be familiar with surgical procedures and techniques involving pelvic floor repair and non absorbable meshes before employing GYNECARE PROLIFT+M Pelvic Floor Repair Systems.
>
> • Acceptable surgical practices should be followed in the presence of infected or contaminated wounds.

• Post-operatively the patient should be advised to refrain from intercourse, heavy lifting and/or exercise (e.g. cycling, jogging) until the physician determines when it is suitable for the patient to return to her normal activities.

• Avoid placing excessive tension on the mesh implant during placement.

• Refer to the recommended surgical technique for the GYNECARE PROLIFT Pelvic Floor Repair System for further information on the GYNECARE PROLIFT procedures.

• Use the GYNECARE PROLIFT+M Pelvic Floor Repair Systems with care, and with attention to patient anatomy and proper dissection technique, to avoid damage to vessels, nerves, bladder, bowel and vaginal wall perforation.

• Transient leg pain may occur and can usually be managed with mild analgesics.

• Do not remove the GYNECARE PROLIFT Cannulas from the patient until the mesh implant has been properly positioned.

It would be almost impossible for a manufacturer to list the exact frequency and severity of dyspareunia in the IFU, as those can fluctuate daily. The same can be said for mesh exposure, recurrence, urinary problems, and various other complications that are well documented in the medical literature. Ethicon was diligent in tracking, monitoring, and analyzing safety data from reported complications and medical literature.

It is my opinion, to a reasonable degree of medical certainty, that the applicable Prolift IFU at the time, as well as the Prolift+M IFU which incorporated and was supplemented by professional education and the surgical technique guide, warned pelvic surgeons of the appropriate risks and complications related to the Prolift & Prolift+M. Pelvic floor surgeons who would have the licensing, credentials, and privileges to perform the Prolift & Prolift+M, would be aware of the risks and complications that can occur with any pelvic surgery. These include but are not limited to: pain and dyspareunia, both of which can be short term or chronic, and voiding dysfunction. Pelvic floor surgeons would be aware of such risks, and should be confident in their ability to manage complications from the procedures they feel competent to perform, based on their medical training, medical literature, their clinical experience, professional education, and through the Prolift & Prolift+M IFU/Technique Guide/Surgeon's Monograph. Training on mesh properties, counseling patients using evidence based-medicine, and managing complications from prolapse surgeries involving mesh is included in various training guidelines and curricula for residents and fellows.

The FDA provided an update on surgical mesh in July 2011. It determined "that serious complications are not rare", contrary to what was stated in the 2008 *PHN*, and "transvaginally

placed mesh in POP repair does not conclusively improve clinical outcomes over traditional non-mesh repair."

In response to the FDA's communication, in November 2011, the American Urological Association (AUA)'s position statement that "**certain patients may benefit from mesh techniques"** and the use of mesh should be a choice made after a careful discussion between surgeon and patient. Better data are needed to determine the appropriate role of vaginal mesh technique in the treatment of POP. It is also important "**that many of these complications are not unique to mesh surgeries and are known to occur with non mesh POP procedures as well**". The AUA in 2011 stands by their 2009 AUA guideline for the Surgical Management of Stress Urinary Incontinence which concluded that "**synthetic slings are an appropriate treatment for women with stress incontinence with similar efficacy but less morbidity than conventional non mesh sling techniques**".

In December 2011, the American College of Obstetrician and Gynecology (ACOG) along with the American Urogynecologic Society (AUGS) published their committee opinion. Recommendations that outcomes, both objective and subjective, should be defined and that complications and reoperation rates should be reported as outcomes. POP vaginal mesh repair should be reserved for high risk individuals. Surgeons should undergo specialized training. Compared to existing mesh products and devices, new products should not be assumed to have equal or improved safety unless clinical long term studies are available. **They support continued audit and review as well as a registry for all current and future vaginal mesh implants**. They recommend rigorous comparative effectiveness studies and lastly that patients should provide their informed consent after reviewing the risks and benefits of the procedure as well as discussing alternative repairs. **They did not recommend abandonment of vaginal mesh augmentation for POP surgery.**

In 2012, the consensus of the 2nd IUGA grafts round table acknowledged the large number of traditional techniques of pelvic surgery with many variations from one surgeon to another, with no available data to achieve standardization. **They recognized the need for tissue reinforcement and established patient risk factors where mesh could potentially be beneficial**. They also concluded that "**the main factor for the development or persistence of problematic post-operative pain is the presence of pain preoperatively**"

In March of 2013, the AUGS' position on restriction of surgical options for pelvic floor dysfunction stated that "**A complete restriction on the use of surgical mesh safety was not the intent of the FDA communication**". The decision on surgical alternatives should be made by the patient and her surgeon. "**A ban on surgical mesh would prohibit the surgical studies mandated by the FDA and recommended by the NIH, ACOG and AUGS. In some**

circumstances, transvaginal mesh for pelvic organ prolapse may be the most appropriate surgical option… Any restriction of mesh slings for stress urinary incontinence is clearly not supported by any professional organization or the FDA… Instead of a ban on mesh we recommend the implementation of credentialing guidelines so that mesh procedures are performed by qualified surgeons". Even on the FDA's website stated in 2013 that "the safety of multi-incision slings is well established in clinical trials that followed patients for up to 1 year." (FDA, 2013). In June 2016, they revised their position on mesh, stating "**we are concerned that the multimedia attention has resulted in confusion, fear and an unbalanced negative perception regarding the mid-urethral sling as treatment for stress urinary incontinence**"…"Polypropylene is safe and effective as a surgical implant"

The FDA's decision in 2016 to reclassify mesh from Class II to Class III was foreseeable. This order does not affect mesh used for stress urinary incontinence or abdominally placed mesh. It does require all new products to submit pre-market approval application and orders manufacturers of current products to submit post-market analysis within 30 months.

The FDA, in January 2017, issued a final reclassification order regarding surgical instruments for use with urogynecologic surgical mesh from Class I to Class II. This includes needle passers, trocars, needle guides and various tissue anchors used in vaginal or abdominal pelvic prolapse surgery and incontinence surgery. Some of these devices, in use for years, have dual properties for use with vaginally or abdominally placed mesh, and sutures for native tissue repair.

In addressing the FDA's statement that "serious mesh complications are not rare", one must define what constitute a serious adverse event. An article addressing the criticisms of the FDA's 2011 analysis demonstrates the views held by a large body of pelvic floor surgeons who also signed on in support of the article (Murphy, 2012 – Time to Rethink: an evidence-based response from pelvic surgeons to the FDA Safety Communication: "Update on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse."). These include death or life threatening complications, those that require inpatient hospitalization or increased length of stay of more than 24 hours and complications resulting in disability or permanent damages with significant impairment of conducting normal life functions or an intervention required to prevent any of the above. Most vaginal mesh exposures do not constitute a serious complication as approximately 50% will be treated with vaginal cream and the remainder will be treated by excision in the office or in a surgical suite, many as out patients. One must keep in mind that since most studies do show better anatomical support with vaginal mesh, if given enough time, the native tissue failures will require a return to the operating room for major repeat surgeries, with increased morbidity to previous scar tissue and patient age. We may ask then: would this not constitute a readmission? And should it not be considered serious adverse event? Mesh erosions from sacrocolpopexy have been reported up to 10.5% at 7 years. These results were published in 2013, after the FDA's 2011 update. Native tissue repairs have

complications of suture exposure, erosion, granuloma, injuries from the surgical instruments that introduce these sutures, along with scarring and dyspareunia. Sacrocolpopexy, often considered the gold standard for the management of apical vaginal or uterine prolapse, also has risks of dyspareunia and pain even without exposure along with other intra-abdominal surgical complications. Non-synthetic grafts and permanent sutures or tacks can also erode as shown by the earlier mentioned SGS systematic review by Abed. Overall the rate of serious adverse events occurring after transvaginal mesh, sacrocolpopexy and traditional repair are comparable (Lowman, 2016).

The IFUs for Prolift and Prolift+M list the complications that are specific to the use of the device. Mesh degradation, chronic inflammation, and cytotoxicity are not considered complications. I have not seen in my practice or in the peer-reviewed medical literature any signs of or clinical significance attributed to alleged degradation or cytotoxicity of either Prolift or Prolift+M. The potential for "degradation of the polypropylene which weakens the mesh to the point that it literally falls apart during dissection" (Ostergard, 2016) is contrary to his own theory of how the mesh reacts within the body, migration of cells in the interstices, collagen and scarring. With new understanding of the process to clean explanted mesh, the previously seen "flakes" on electron microscope attributed to degradation are washed away revealing a smooth surface. If there was degradation, the cracked surfaces seen on the blue fibers would have been blue, not white and once removed, the original fiber would have been pitted or had some residual irregularity on the surface (Ong, 2016; Thames, 2016). The authors noted in the disclosure of the published study that they have provided litigation consulting services to Ethicon, Inc. The authors concluded, based on well-designed methodology and testing, that "[o]ur effective cleaning of explanted Prolene meshes and subsequent analyses showed that they did not degrade in vivo, confirming the in vivo stability of properly formulated polypropylene. Instead, the cracked layer that some researchers have identified as degraded Prolene is an adsorbed protein–formaldehyde coating, resulting from the well-established formalin–protein fixation process, which occurs immediately upon placing an explant in formalin." Mesh weakening and falling apart is contrary to the massive documentation in the literature, as well as the clinical experience and surgical success using polypropylene sutures or mesh. If polypropylene mesh behaved in this manner, weakened and fell apart, abdominal walls would be bulging out and hernia mesh would not be considered as standard of care for most hernia repair. If polypropylene behaved in this manor, vaginal apexes would be descending at an alarming rate and sacrocolpopexy would have never been considered for gold standard in level 1 suspension. If polypropylene behaved in this manner, millions of women would suddenly return to urethral hypermobility and stress urinary incontinence. Heart surgeries using Prolene sutures would not provide years of success if Prolene degraded. Many of my colleagues, as well as myself have revised, transected and resected polypropylene slings and meshes and have never encountered this "degradation" after primary insertion of mesh. I have also had to enter the abdomen through polypropylene sutures, placed decades prior, and found the suture and original knot intact.

What is known is that all surgeries will initiate an inflammatory response, which is essential for healing, eventual tissue remodeling and scarring. As surgeons, we know this from medical school, from our residency training and our own surgical experiences. As graft material was developed first for abdominal hernia repair then used for sacrocolpopexy and finally introduced vaginally, the risks associated with each type, biological or synthetic, have been well described. A host response to a foreign body is well described and will include acute followed by chronic inflammation, granulation and encapsulation. With macroporous mesh, this occurs at the outside periphery of the fiber, and is snot systemic (Moalli, 2014).

Published reports attempting to evaluate or quantify the levels of inflammation have many inconsistencies and some of the techniques to preserve, transport and clean the various specimens may have contributed to abnormal findings if the mesh. Hill (2015) examined explanted slings but 43.8% had used various "conservative measures" and 31.6% had prior unsuccessful attempts at removal. The most common finding was mild inflammation and moderate fibrosis. Mellano (2016) reported cultures from explanted sling through vaginal surgery. They only demonstrated low density bacterial colonization without any difference whether the mesh had been removed after a recent or chronic erosion or if the mesh was removed for voiding dysfunction or urinary tract infection with intact coverage. There was also no difference in culture comparing the contaminated exposed mesh when compared to a site of non-exposed mesh. This demonstrates possible vaginal contamination during surgery but also that despite having mesh exposure, in a contaminated environment, the mesh actually does not promote infection. Smith (2013) noted "relatively minimal inflammation," low rates of granulation (6.3%), and benign reactive changers with fibrosis in 70% of explants, with fibrosis being a major component of any scar.

As far as the carcinogenic properties of polypropylene, there has never been a causal effect documented (King, 2014). The one case of a clear cell carcinoma associated with chronic inflammation occurring near the site of a sub urethral sling mesh exposure, does not mean causation. Additionally, there is no reliable evidence that supports a causal connection of Prolift or Prolift+M to cancer. Prolene suture material has been FDA approved and utilized in many different surgeries in different areas of the body for over 50 years with high safety record. All over the world, in men and women, billions of sutures since the 1970's have been used in cardiovascular and ophthalmic surgery, neurosurgery, plastic and reconstructive surgery, as well as general, urological and gynecological surgery. Tens of millions of polypropylene hernia meshes have been inserted since the 1980's. Over three million suburethral sings and hundreds of thousands of apical and vaginal meshes have been used, without any evidence of systemic disease or associated cancer (King, 2014 - Moalli, 2014 - Linder, 2016 – Adel 2016). The fact that the Oppenheimer effect was described in rats using various plastic disks in 1958, does not apply to humans and not in the filament or meshes that have been in use for decades. Millions of fibers of Prolene sutures have been in use since the 1960's, over 3 million women have had their incontinence cured by slings, millions of polypropylene meshes have been implanted for various

hernia and prolapse surgeries around the world. If polypropylene was toxic or caused cancer, we would have seen evidence of this by now. The MSDS warnings, required by OSHA, of sarcoma formation and that polypropylene is not to be implanted in humans are statements meant for the manufacturers and handling of the raw materials. These statements are made due to liability concerns in the production of the final product (Moalli, 2014). An attempt to induce genomic instability after exposure failed (Webber,). The Agency for Research on Cancer found no evidence of tumorigenicity of metallic or synthetic implants in humans.

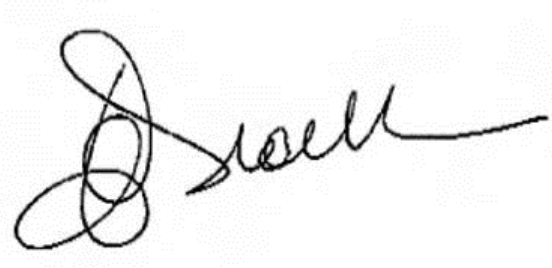
The medical literature along with clinical experience in residency, fellowship for some, and in actual practice, are typically how surgeons get information about frequency and severity of complications. Through my training and experience, review of the medical literature, discussions with colleagues, experience with teaching procedures to others, and my review of FDA documents, society statements, and clinical guidelines, complications such as urinary problems, incontinence or retention, dyspareunia, pain and scarring are well-known complications that can occur with any pelvic floor surgery for the treatment of pelvic organ prolapse and/or stress urinary incontinence. We are taught this as early as medical school and it is discussed throughout surgical and gynecological residency. These complications are basic, elemental pelvic surgery risks and are not unique to Prolift and Prolift+M. Performing surgery is always a balance between risks and benefits and there are no risk-free surgeries. Even the most minor mundane procedure carries a risk of a significant adverse outcome. People have died as a result of a paper cut. The complications that are unique to Prolift and Prolift+M involve complications from the mesh itself and its surgical introduction, which are clearly described in the IFU and professional education materials. What cannot be accurately predicted is how a particular patient will react to a particular surgical procedure or implant. Surgeons are expected to practice evidence based medicine and to counsel their patients about the frequency and severity of complications reported in the medical literature and their clinical experience, all while determining the goals of the patient, their risk tolerance, and their capacity to understand risk information.

Prolift and Prolift+M had utility to surgeons because of its usability and reproducibility as well as its anatomic correction of prolapsed organs, significant improvements in objective cures with non-inferiority in subjective cures and quality of life, and acceptable and manageable complication risk profile. It is minimally invasive compared to laparotomy and utilized mesh constructed of material which had been in use in the field for 50 years before it.

The level 1 suspension of the proximal Posterior Prolift and Prolift+M to the sacrospinous ligament (SSL) is built on surgical techniques that had been in place in the field for decades. Overall the design of the Posterior Prolift and Prolift+M not only made sense, but it was consistent with the decades-long march towards optimizing correction of prolapse with adjunct material and was state of the art.

The Prolift and Prolift+M system offered advantages of shorter surgical times for combined posterior and apical support, eliminating the need for difficult suturing compared to vaginal Sacrospinous fixation or McCalls culdoplasty. Further, the durability of mesh repairs, such as Prolift & Prolift+M, provided surgeons with a level of predictability and consistency over native tissue repairs, which rely on sewing together damaged tissues. Pelvic floor surgery has always carried a risk of complication, but these risks are commonly known in the medical community of surgeons who perform prolapse surgeries.

In conclusion, Prolift and Prolift+M are reasonably safe for the intended use in treating pelvic organ prolapse when used by an experienced surgeon in an appropriately selected and patient. Although Ethicon decommercialized these products in 2012 for business reasons, independent clinical studies continue to demonstrate the long-term safety and efficacy of these devices.



Julie Drolet, MD

Date: February 1, 2017